APPENDIX A
ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: September, 2001
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2h
Species: Rabbits

Minimal Risk Level: 0.2 [ ] mg/kg/day [X] mg/m^3

Reference: Weeks MH, Lawson MA, Angerhofer RA, et al. 1977. Preliminary assessment of the acute toxicity of malathion in animals. Arch Environ Contam Toxicol 6:23-31.

Experimental design: The purpose of the study was to compare the acute effects of two different malathion aerosols on the activity of plasma and erythrocyte (RBC) cholinesterase from rabbits. Groups of male New Zealand rabbits (6/exposure level) were exposed for 6 hours to 0 (chamber air), 6, 34, 65, or 123 mg malathion/m^3 as an aerosol generated from a technical malathion formulation (95% pure). Blood was collected at 10 minutes and 24, 72 hours, and 7 days post exposure for determination of cholinesterases activities. Tissues were also removed for histopathological examination. In a parallel experiment, rabbits were similarly exposed to aerosols generated from a formulation containing 6% malathion and a fuel oil mixture. The malathion concentration in the air in the latter case was 0 (controls), 8, 24, 30, 66, or 128 mg/m^3.

Effects noted in study and corresponding doses: There were no signs of toxicity or deaths in the group exposed to 95% technical malathion. Exposure to 128 mg/m^3 aerosol generated from the 6% formulation resulted in four out of six rabbits dying 24 hours after exposure. Exposure to the highest concentration of the 95% formulation inhibited plasma cholinesterase by 37% 24 hours post exposure and 41% 72 hours post exposure. No other significant differences were seen. RBC cholinesterase was inhibited by 38%, 48%, and 48% by the high exposure concentration 24 hours, 72 hours, and 7 days post exposure, respectively. Exposure to the aerosol generated from the 6% formulation resulted in 38% inhibition of plasma cholinesterase with the 66 mg/m^3 concentration 72 hours after exposure and 71% inhibition with the 128 mg/m^3 concentration 10 minutes post exposure. With this formulation, RBC cholinesterase was inhibited 61% and 46% with the 128 mg/m^3 concentration 10 minutes and 24 hours, respectively, post exposure. Without providing any further details, the authors stated that exposure to malathion caused no histopathological alterations in the organs examined (not specified).

Exposure concentration and end point used for MRL derivation: 65 mg/m^3; NOAEL for neurological effects (inhibition of RBC cholinesterase activity).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from humans to animals

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration:
A human equivalent concentration was not determined due to lack of information on the size distribution of the aerosol particles in the study.

Was a conversion used from intermittent to continuous exposure?
Yes, 6/24.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. A 42-day controlled-exposure study in volunteers reported nasal and eye irritation after 5-10 minutes of exposure to 85 mg/m^3 malathion (Golz 1959); subjects were exposed 2 hours per day. Neither plasma nor RBC cholinesterase activities were significantly altered during the study.

Agency Contact (Chemical Manager): Jewel D. Wilson, Ph.D.

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: September, 2001
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 4r
Species: Rat

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] mg/m^3

Reference: Beattie G. 1994. A 13-week toxicity study of aerolized malathion administered by whole body inhalation exposure to the albino rat: Lab project No: 90729. Unpublished study prepared by Product Safety Assessment, Bio-Research Labs, Ltd. MRID 43266601.

Experimental design: Groups of male and female Sprague-Dawley rats (15/sex/exposure level) were exposed whole body to malathion (96.4% pure) aerosols at concentrations of 0 (air control), 100, 450, or 2010 mg/m^3 6 hours/day, 5 days/week, for 13 weeks. Rats were monitored for clinical signs and body weight changes. At termination, gross necropsies were conducted and tissues (unspecified in the summary available) were processed for microscopical evaluation. Cholinesterase activity was determined in plasma, red blood cells (RBC), and brain.

Effects noted in study and corresponding doses: There were no malathion-related effects on survival, body weight, or food intake. Adverse clinical signs consisting of urogenital staining , excessiv esalivation, and ungroomed fur were seen mostly in the high-exposure group, but also occurred in sporadically in the other exposed groups. I appears that histopathological treatment-related alterations were restricted to the respiratory epithelium. Exposure-concentration-related lesions in the nasal cavity and the larynx of both sexes were seen. The lesions in the nasal cavity consisted of slight to moderate degeneration and/or hyperplasia of the olfactory epithelium. The lesions in the larynx consisted of epithelial hyperplasia with squamous keratization seen in some rats. The effects on cholinesterase activities were concentration-related and effects on females seemed more pronounced than in males. Plasma cholinesterase activity was decreased 30% and 70% in the mid-level and high-level females, respectively. RBC cholinesterase activity was decreased 22% and 27% in mid-level males and females, respectively, and 43% and 44% in high-level males and females, respectively. Brain cholinesterase activity was decreased 41% in high-level females.

Exposure concentration and end point used for MRL derivation: 100 mg/m^3; LOAEL for respiratory effects (hyperplasia of the olfactory epithelium and of the larynx epithelium).

[] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: A human equivalent concentration was not determined due to lack of information on the size distribution of the aerosol particles in the summary of the study available.

Was a conversion used from intermittent to continuous exposure?
Yes, 5/7 x 6/24.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). A 42-day controlled-exposure study in volunteers exposed to up 85 mg/m^3 malathion 2 hours/day reported no signs of toxicity during the study except for occasional nose and eye irritation 5-10 minutes into the exposure session (Golz 1959). No significant changes in plasma or RBC cholinesterase activities were seen throughout that study.

Agency Contact (Chemical Manager): Jewel D. Wilson, Ph.D.

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: July 19, 2001
Profile Status: Third Draft Pre Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 70
Species: Humans

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Moeller HC, Rider JA. 1962. Plasma and red blood cell cholinesterase activity as indications of the threshold of incipiente toxicity of ethyl-p-nitrophenyl thionobenzenephosphorate (EPN) and malathion in human beings. Toxicol Appl Pharmacol 4:123-130.

Experimental design: A three-phase study was conducted in humans. In the first phase, five male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days. In the second phase, which started 3 weeks after the first phase had terminated, five male volunteers received daily capsules with malathion providing about 0.23 mg malathion/kg/day for 47 days. In the third phase, five new subjects received approximately 0.34 mg malathion/kg/day for 56 days. Plasma and red blood cell (RBC) cholinesterase was determined twice weekly before, during, and after administration of malathion. Routine blood counts and urinalyses were conducted at the end of each study period.

Effects noted in study and corresponding doses: Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity, nor did it alter blood counts or urinalyses, or induce clinical signs. In phase three, 0.34 mg malathion/kg/day for 56 days caused a depression of about 10% in plasma cholinesterase activity during treatment and a maximum depression of about 25% approximately 3 weeks after cessation of treatment. RBC cholinesterase activity did not appear to be significantly affected during treatment, but was depressed also by about 25% 3–4 weeks after treatment with malathion ceased. No clinical signs were seen in the volunteers.

Dose and end point used for MRL derivation: 0.23 mg/kg/day; NOAEL for neurological effects (inhibition of plasma and RBC cholinesterase activities).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from humans to animals
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. The study by Moeller and Rider (1962) was the only available study of controlled ingestion of malathion in humans for review. Most of the studies in animals, while supporting the human data, have been conducted with higher dose levels of malathion.

Agency Contact (Chemical Manager): Jewell D. Wilson, Ph.D.

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: July 19, 2001
Profile Status: Third Draft Pre Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 92r
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Daly I. 1996a. A 24-month oral toxicity/oncogenicity study of malathion in the rat via dietary administration: Final Report: Lab Project Number:90-3461:J-11 90-3641 Unpublished study prepared by Huntington Life Sciences. MRID 43942901.

Experimental design: Groups of male and female Fischer-344 rats (90/sex/dose level) were administered malathion (97.1%) in the diet at levels of 0, 50/100, 500, 6,000, or 12,000 ppm for 2 years. The lowest dietary concentration was reduced from 100 to 50 ppm because of inhibition of RBC cholinesterase activity. The mean intakes of malathion estimated by the investigator were approximately 0, 2, 29, 359, or 739 mg malathion/kg/day to males and 0, 3, 35, 415, or 868 mg/kg/day to females. Ten rats/sex/group were sacrificed at 3 and 6 months primarily for ocular tissue evaluation. Additional sacrifices were conducted at 12 months for more complete assessments. End points evaluated included clinical signs, body weight, food consumption, hematology and clinical chemistry, and gross and microscopical appearance of main tissues and organs.

Effects noted in study and corresponding doses: Administration of malathion significantly increased mortality in males at 6,000 ppm and in both sexes at 12,000 ppm. Body weight gain was reduced both in males and females at the two highest exposure levels, but food intake was not decreased. Hemoglobin, hematocrit, mean corpuscular volume (MCV) and mean cell hemoglobin were reduced also in both sexes at the two highest dietary levels of malathion in both males and females. Absolute and relative liver and kidney weights were increased in males and females from the 6,000 and 12,000 ppm groups. Relative absolute thyroid and parathyroid weights were increased in males at 6,000 ppm at 12 months and in females at 6,000 and 12,000 ppm at termination. At 24 months, at the 500 ppm malathion dietary level (29 mg/kg/day for males, 35 mg/kg/day for females), plasma cholinesterase activity was reduced 29 and 18% in males and females, respectively, RBC cholinesterase was reduced 17 and 27%, respectively, and brain cholinesterase was reduced 3 and 1%, respectively. At the 6,000 ppm level, plasma cholinesterase in males and females was reduced 64 and 61%, respectively, and brain cholinesterase was reduced 21 and 18%, respectively. No significant reduction in enzyme activities was observed at the lowest dietary level of malathion, 2 mg/kg/day for males and 3 mg/kg/day for females.

Dose and end point used for MRL derivation: 2 mg/kg/day; NOAEL for neurological effects (inhibition of RBC cholinesterase activity).

[X] NOAEL [] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, conversions from dietary ppm to mg/kg/day doses was done by the study author.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. No data were located regarding effects of chronic oral exposure to malathion in humans. Few additional long-term studies have been conducted with malathion in rats and mice (NCI 1978, 1979a; Slauter 1994), but the one by Daly (1996a) used the widest dose range. The studies conducted by NCI (1978, 1979a) did not measure cholinesterase activities. An 18-month dietary study in mice identified a NOAEL of approximately 20 mg/kg/day for plasma and RBC cholinesterase inhibition (Slauter 1994), and this was the highest NOAEL below a LOAEL. However, ATSDR's policy and guidance for MRL derivation is to always use the most sensitive species and the database indicates that rats are more sensitive than mice for malathion.

Agency Contact (Chemical Manager): Jewell D. Wilson, Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) <u>CEL</u> Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) <u>Estimated Upper-Bound Human Cancer Risk Levels</u> This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) <u>Key to LSE Figure</u> The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6 **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

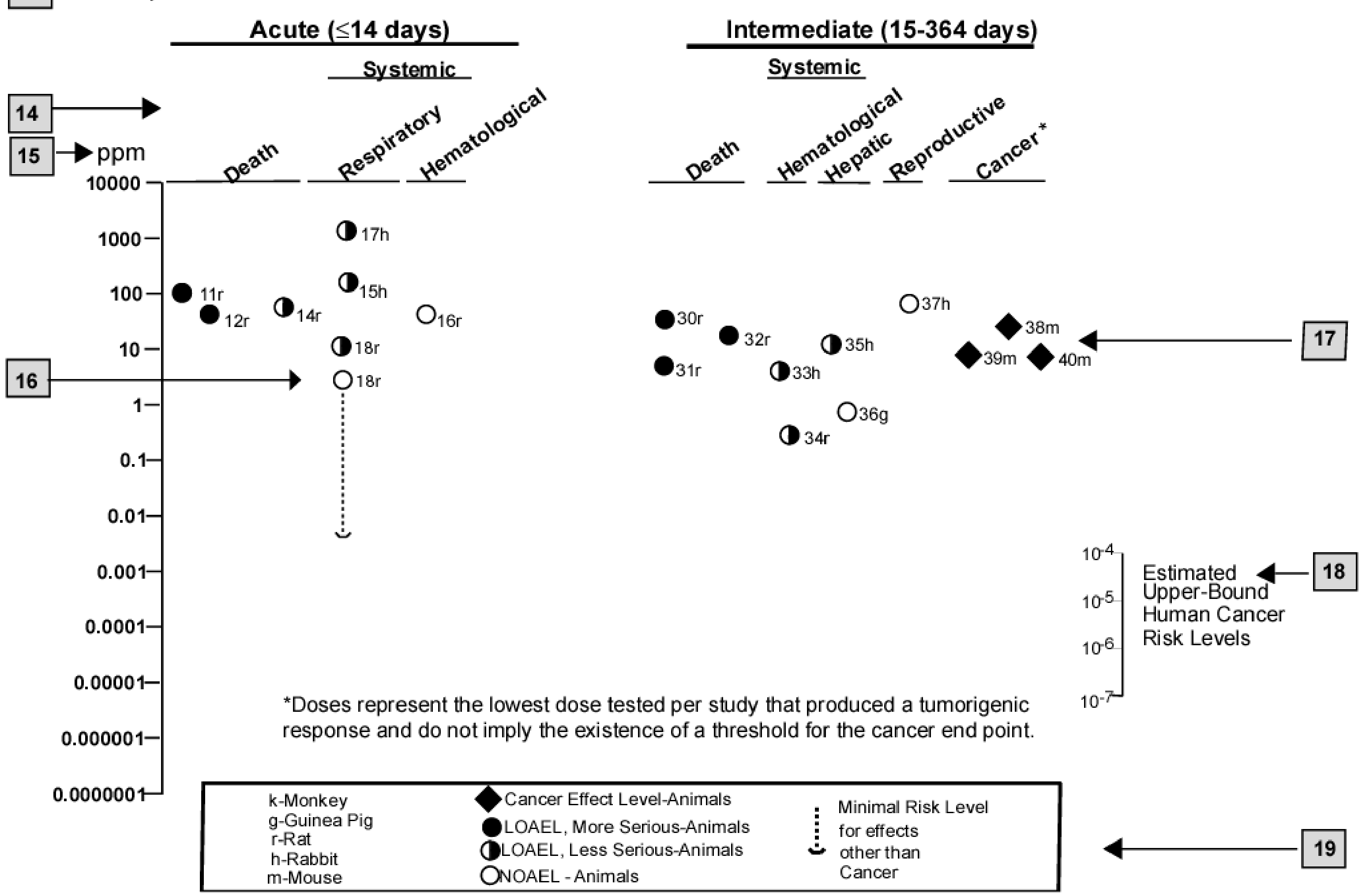
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer						9	
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram

EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter

mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram

pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram

q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX

APPENDIX D